developing aGVHD may be started on treatment preemptively. Among biomarkers identified in current study, only ST2 was prognostic of aGVHD risk before day +14 after hematopoietic cell transplantation; this is not surprising given the relatively late (median, 36 days) onset of aGVHD after NMAT. Clinically relevant prognostic tools proposed in prior studies consisted of a panel rather than a single biomarker; therefore, combinations of biomarkers need to be explored further [1,2,9].

In conclusion, the current study identified ST2, REG3α, and elafin as prognostic biomarkers to stratify for risk of developing aGVHD after Cy/Flu-based NMAT. These results need to be confirmed in a large independent validation cohort, ideally among a number of institutions, to establish clinically useful cut-offs for their future use in clinical trials.

ACKNOWLEDGMENTS

The authors thank the patients who participated in this study, the clinicians of Indiana University Bone Marrow and Stem Cell Transplantation Program, and the members of the Paczesny and Orschell laboratories.

Financial disclosure: Supported by the National Institutes of Health grant R01CA174667 (to S.P.) and the Lilly Physician Scientist Initiative Program (to S.P.) (grant number 20091568000).

Conflict of interest statement: S.P. holds a patent on "methods of detection of graft-versus-host disease" (US Patent 13/573,766).

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Brentuximab Vedotin Is Associated with Improved Progression-Free Survival after Allogeneic Transplantation for Hodgkin Lymphoma

Robert Chen [1,*], Joycelynne M. Palmer [2], Ni-Chun Tsai [2], Sandra H. Thomas [1], Tanya Siddiqi [1], Leslie Popplewell [1], Len Farol [3], Auayporn Nademanee [1], Stephen J. Forman [1]

[1] *Department of Hematology/Hematopoietic Cell Transplantation, City of Hope, Duarte, California*
[2] *Division of Biostatistics, City of Hope, Duarte, California*
[3] *Bone Marrow Transplantation Program, City of Hope–Kaiser Permanente, Los Angeles, California*

Article history:
Received 5 May 2014
Accepted 30 June 2014

Key Words:
Allogeneic transplantation
Reduced-intensity
Hodgkin lymphoma
Brentuximab vedotin

A B S T R A C T

We previously reported that brentuximab vedotin (BV) enabled successful reduced-intensity allogeneic hematopoietic cell transplantation (RIC-alloHCT) in patients with relapsed Hodgkin lymphoma, after a median follow-up of 14.4 months. We now provide an updated report on 21 patients who were treated from 2009 to 2012 with BV before RIC-alloHCT with a uniform fludarabine/melphalan conditioning regimen and donor source after a median follow-up of 29.9 months. We have also retrospectively compared the patient characteristics and outcomes of these BV-pretreated patients to 23 patients who received fludarabine/melphalan RIC-alloHCT without prior BV, in the time period before the drug was available (2003 to 2009). Patients who were treated with BV before RIC-alloHCT had a lower median hematopoietic cell transplantation–specific comorbidity index and a reduced number of peri-transplantation toxicities. There were also improvements in 2-year progression-free survival (59.3% versus 26.1%) and cumulative incidence of relapse/progression (23.8% versus 56.5%).

INTRODUCTION

Brentuximab vedotin (BV) is an antibody-drug conjugate of anti-CD30 antibody and the microtubule-disrupting agent, monomethyl auristatin E [1]. BV is approved for use in Hodgkin lymphoma (HL) patients who have failed autologous hematopoietic cell transplantation (autoHCT). Phase II studies report

Financial disclosure: See Acknowledgments on page 1867.

* Correspondence and reprint requests: Robert Chen, MD, Department of Hematology/HCT, City of Hope, 1500 E. Duarte Road, Duarte, CA 91010.
E-mail address: rchen@coh.org (R. Chen).

1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.06.037

an overall response rate of ~75% with an acceptable safety profile [2,3]. We previously published our findings on the use of reduced-intensity (RIC) allogeneic hematopoietic cell transplantation (alloHCT) in 24 relapsed/refractory patients with HL [4], yielding a 2-year progression-free survival (PFS) of 27% (95% confidence interval [CI], 22% to 32%). We have also reported early data showing that BV salvage before RIC-alloHCT results in a 1-year overall survival (OS) of 100% and PFS of 92.3% (95% CI, 61.3% to 98.8%) in patients with relapsed HL [5]. We now report on a more homogenous Hodgkin patient population, with extended follow-up for outcomes of RIC-alloHCT after BV salvage. Additionally we have retrospectively compared the outcomes of these patients to a consecutive case series of BV-naïve patients who underwent RIC alloHCT in the pre-BV era. Our hypothesis is that BV salvage therapy could deliver patients who are better candidates for transplantation, via higher response rates and lower toxicity, thus contributing to improved outcomes after RIC-alloHCT.

PATIENTS AND METHODS

The City of Hope Institutional Review Board approved the retrospective analysis of data from a consecutive case series of 23 HL patients who underwent RIC-alloHCT with no prior BV exposure (no-BV group) between January 2003 and July 2009 (pre-BV era) and a consecutive case series of 21 HL patients who received BV before RIC-alloHCT (BV group) from July 2009 to December 2012. Sixteen of the 21 HL patients who received BV were enrolled on prospective clinical trials (4 separate trials). None of the 23 HL patients without prior BV exposure received BV at relapse after RIC-alloHCT. Eligible patients were $\geq$ 18 years old with histologically confirmed HL expressing CD30, who had relapsed after previous autoHCT or were not autoHCT candidates. Patients were excluded if they had received a previous alloHCT. All patients received fludarabine/melphalan (fludarabine 25 mg/m^2 $\times$ 5 days followed by melphalan 140 mg/m^2 $\times$ 1 day) as their transplantation conditioning regimen. Only matched related sibling donor and matched unrelated donor transplantations were included; haploidentical and cord blood transplantations were excluded. Comorbid conditions at the time of alloHCT were scored using the hematopoietic cell transplantation–specific comorbidity index (HCT-CI) [6]. The Bearman scale [7] was used to capture toxicities associated with RIC-alloHCT. Baseline patient characteristics for the 44 patients are summarized in Table 1.

Post-transplantation evaluation of disease status with imaging studies, bone marrow biopsies, and engraftment analysis occurred at 30 days, 100 days, and 1 year after transplantation and yearly thereafter, or as clinically indicated. HL disease response was scored using standard criteria [8]. OS and PFS probabilities were calculated using Kaplan-Meier [9] (differences assessed by log-rank test) and cumulative incidence of relapse/progression and nonrelapse mortality (NRM) were calculated as competing risks [10] (differences assessed using the Gray method).

RESULTS

There were no significant baseline differences between the 2 groups in terms of age, disease stage at diagnosis, response to induction, number of prior therapies, donor type, stem cell source, and time from diagnosis to RIC-alloHCT. The patients in this study represent a heavily pretreated population in which the majority of patients had undergone high-dose chemotherapy and autoHCT; the median number of prior regimens was 4. The ratio of matched related donors to matched unrelated donors in each group was roughly one half. Graft-versus-host disease (GVHD) prophylaxis differed slightly between the 2 groups because of an institutional shift to tacrolimus/sirolimus in 2005. Although the median number of prior regimens was the same, the no-BV group received more combination chemotherapy and radiotherapy (Table 1). The 2 groups also differed in terms of disease status at the time of RIC-alloHCT and HCT-CI score. The median HCT-CI score was significantly better in the BV group (0 versus 2, $P < .01$) and patients in this group were also more likely to be in complete remission before RIC-alloHCT (28.6% versus 4.3%, $P = .04$).

Table 1
Patient, Disease, and Treatment Characteristics

Characteristics	BV N = 21	No-BV n = 23
Age, median (range), yr	31 (22-55)	37 (16-63)
Disease stage at diagnosis		
I-II	9 (43)	11 (48)
III-IV	11 (52)	11 (48)
Unknown	1 (5)	1 (4)
Response to induction		
Refractory	5 (24)	7 (30)
Relapsed	16 (76)	16 (70)
No. previous regimens, median (range)	4 (3-6)	4 (3-6)
Previous regimens		
Induction-ABVD	19 (90)	19 (83)
Salvage chemo before autoHCT		
ICE	17	16
ESHAP	2	10
Others	1	2
AutoHCT	19	19
Salvage chemo after autoHCT		
ICE	4	3
ESHAP	0	5
Gemcitabine based	14	17
Bendamustine	3	0
Others	4	9
Radiotherapy	10	17
Consolidation	9	12
Treatment for relapse/refractory	1	5
Time from diagnosis to HCT, median (range), mo	60.6 (13.8-258.3)	36.4 (13.6-214.7)
Intermittent therapy between BV and alloHCT	7	N/A
Gemcitabine based	5	
ICE	1	
Bendamustine	3	
XRT	1	
No. cycles of BV, median (range)	7 (2-16)	0
Best response to BV		NA
CR	6 (29)	
PR	14 (67)	
SD/PD	1 (5)	
Disease status at end of BV		NA
CR	4 (19)	
PR	7 (33)	
SD/PD	10 (48)	
Disease status at HCT		
CR	6 (29)	1 (4)
PR	9 (42)	9 (39)
SD/PD	6 (29)	13 (57)
Stem cell source		
Bone marrow	1 (5)	3 (13)
Peripheral blood	20 (95)	20 (87)
HCT-CI score, median (range)	0 (0-3)	2 (0-4)
Type of donor		
MRD	10 (48)	12 (52)
MUD	11 (52)	11 (48)
GVHD prophylaxis		
Tacrolimus/sirolimus	19 (90)	16 (70)
Cyclosporine A/MMF	2 (10)	6 (26)
Tacrolimus/methotrexate	0 (0)	1 (4)

ABVD indicates adriamycin, bleomycin, vinblastine, dacarbazine; ICE, ifosfamide, carboplatin, etoposide; ESHAP, etoposide, cisplatin, Ara-C, methylprednisolone; XRT, radiation therapy; PR, partial response; SD, stable disease; PD, progressive disease; MRD, matched related donor; MUD, matched unrelated donor; MMF, mycophenolate mofetil.
Data presented are n (%), unless otherwise indicated.

There were no significant differences between groups in terms of engraftment or acute/chronic GVHD incidence. All patients engrafted, with median time to absolute neutrophil count $\geq$ 500 cells/μL of 14 days (range, 11 to 21) in the BV

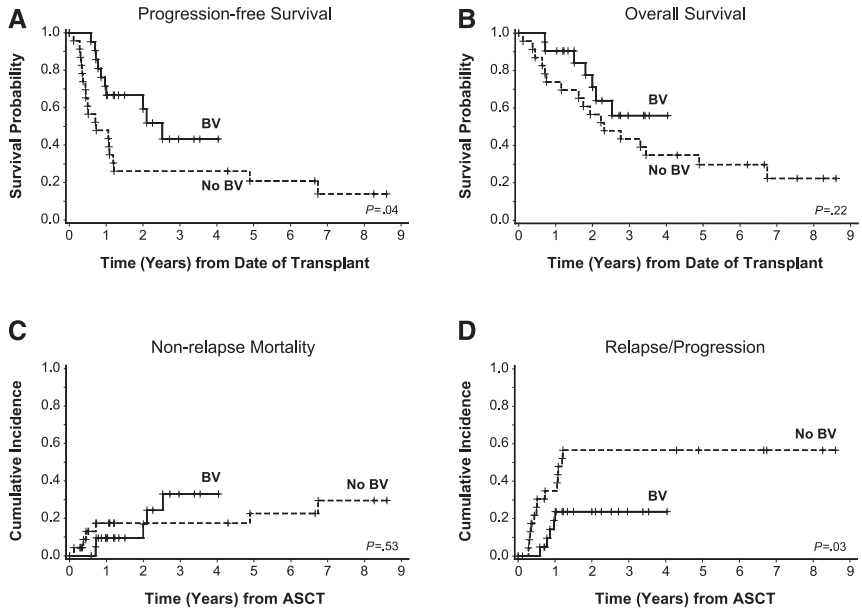

Figure 1. Outcomes. N = 44 patients. Surviving patients in the BV group (n = 21) had median follow-up of 29.9 months, No-BV group (n = 23) had median follow-up of 85.3 months. (A) Shows Kaplan-Meier survival probabilities for PFS for BV group (solid line) and no-BV group (dashed line). PFS was defined as time from stem cell infusion to recurrence, progression, or death from any cause, whichever occurred first. (B) Shows OS for BV group (solid line) and no-BV group (dashed line). OS was measured from stem cell infusion to death from any cause. (C) Shows cumulative incidence of nonrelapse mortality for BV group (solid line) and no-BV group (dashed line). NRM was measured from transplantation to death from any cause other than disease relapse or progression. (D) Shows the cumulative incidence of relapse/progression for BV group (solid line) and no-BV group (dashed line). The cumulative incidence of relapse/progression was defined as time from stem cell infusion to recurrence or progression. Relapse/progression and NRM were calculated as competing risks.

group and 15 days (range, 10 to 20) in the no-BV group. The median time to platelet count >20,000 cells/μL without transfusion support was 13 days (range, 11 to 26) in the BV group and 13 days (range, 8 to 35) in the no-BV group. All patients in both groups achieved > 99% donor chimerism by day +30. Acute GVHD occurred in 7 of 21 patients (33.3%) in the BV group and 13 of 23 patients (56.5%) in the no-BV group. The cumulative incidence of acute GVHD grades II to IV was 23.8% (95% CI, 8.4 to 43.6) in the BV group versus 47.8% (95% CI, 26.2 to 66.7) in the no-BV group ($P = .06$). For chronic GVHD, the 2-year cumulative incidence was 70.0% (95% CI, 43.3 to 85.9) for the BV group and 65.2% (95% CI, 40.0 to 81.9) for the no-BV group ($P = .56$).

Stratified outcome curves are shown in Figure 1. For the BV-treated group, with a median follow-up of 29.9 months (range, 12.4 to 48.5) in surviving patients, the 2-year PFS was 59.3% (95% CI, 33.9 to 77.7), 2-year OS was 71.1% (95% CI, 43.2 to 87), 100-day NRM was 0%, 1-year NRM was 9.5% (95% CI, 2.5 to 35.6), and the 2-year relapse/progression incidence was 23.8% (95% CI, 11.1 to 51.2). Surviving patients in the no-BV group had longer follow-up (median, 85.3 months; range, 51.5 to 103.3) because of the time-period difference. In the no-BV group, the 2-year PFS was 26.1% (95% CI, 10.6 to 44.7), 2-year OS was 56.5% (95% CI, 34.3 to 73.8), 100-day NRM was 4.3% (95% CI, .6 to 29.6), and 1-year NRM was 17.4% (95% CI, 7.1 to 42.4). The cumulative incidence of relapse/progression at 2 years was 56.5% (95% CI, 39.5 to 80.9). The BV group showed improvement in 2-year PFS (59.3% versus 26.1%, $P = .04$) and a reduction in 2-year relapse/progression incidence (23.8% versus 56.5%, $P = .03$) compared with the no-BV group.

We evaluated regimen-related toxicities in both groups using the Bearman toxicity scale through day +100. There were no grade III to IV events in the BV group, and there were 7 grade III events among 4 patients in the no-BV group: bladder (n = 1), gastrointestinal (n = 1), pulmonary/renal (n = 1), and pulmonary/renal/stomatitis (n = 1). In the no-BV group, there were also an increased number of comorbid conditions: median HCT-CI of 2. In the BV group, fewer patients received multiagent salvage chemotherapies, possibly because of substitution of BV for a combination regimen. Indeed, we found that patients in the BV group had a lower median HCT-CI score (median, 0), higher percentage of patients in complete remission (CR) (28.9%), and fewer peritransplantation toxicities (n = 0 grade III to IV events). Of the baseline patient, disease, and treatment characteristics evaluated by Cox univariate analysis, only previous BV exposure (yes/no) (hazard ratio, 2.27; 95% CI, 1.04 to 4.97; $P = .04$) and HCT-CI score (hazard ratio, 1.40; 95% CI, 1.03 to 1.90; $P = .03$) modeled as a continuous variable were predictive of PFS.

DISCUSSION

The median OS of patients who relapse after autoHCT is only 2.4 years [11]. AlloHCT has been the only option that offers the possibility of long-term remission. Unfortunately, this approach is limited by age, performance status, and comorbidities of patients who have been previously exposed to many rounds of combination chemotherapy. Historical data also show a relatively high relapse rate. Some studies report a low 2-year PFS (23% to 32%) for HL patients undergoing alloHCT [4,12,13], whereas others report 4-year PFS in a similar range (24% to 39%) for HL patients undergoing alloHCT [14,15]. This low PFS could result from lack of disease control before alloHCT, as many patients were not in CR or had chemoresistant disease. BV, an antibody-drug conjugate, was granted accelerated approval by the FDA in 2011 for the

treatment of relapsed/refractory HL after failure of auto-HCT [1]. In the pivotal phase II trial that lead to its approval, patients who achieved responses on BV were allowed to come off trial to proceed to alloHCT. We had previously reported on the successful use of BV as a bridge to alloHCT [5]. This report serves to (1) update that experience with longer follow-up, (2) provide a more homogenous patient population, and (3) compare this group with an historical cohort. Patients in the current report had 1 additional year of follow-up and, thus, we are able to provide 2-year PFS data. All the patients in this report received fludarabine and melphalan as a conditioning regimen and had matched related or unrelated donor stem cell sources (no cord or haploidentical donors).

When compared with our own historical cohort (consecutive case series) who received the same conditioning regimens and stem cell sources, we were able to show that BV before alloHCT improves HCT-CI, peri-transplant toxicities, and disease status at alloHCT. We believe that these 2 groups of patients were essentially matched, with the exception of BV exposure. This is evident by their stage, age, response to induction, previous auto-HCT, and median number of previous treatments. All the patients had relapsed/refractory disease before receiving BV in the BV group or before salvage combination chemotherapy in the no-BV group.

In the pivotal phase II trial, BV had a high overall response rate and was well tolerated with a low toxicity profile. The no-BV group had a higher percentage of patients who received ESHAP, a combination of etoposide, methylprednisolone (solumedrol), high-dose cytarabine (ara-C), and cisplatin which is typically a second salvage chemotherapy regimen. For these patients, who were relapsed/refractory to multiple chemotherapy regimens, another round of salvage chemotherapy could cause greater harm than the benefit it adds. Indeed, patients in the no-BV arm had worse HCT-CI scores and more grade III to IV Bearman scale peri-transplantation toxicities. It is also not surprising that more patients in the BV group were in CR at the time of alloHCT (statistically significant). There were some subtle differences between the groups that were not statistically significant. The no-BV group had received more radiation therapy, which could be because of the use of radiation to achieve disease control before alloHCT. The BV group also had longer time to alloHCT. This could be explained by the fact that BV can be given for multiple cycles because of its relative low toxicity profile, whereas multiagent salvage chemotherapies are only given for a maximum of 2 to 3 cycles before alloHCT. Also, some patients who had achieved CR/partial response waited to undergo alloHCT by choice. Not every patient in the BV group proceeded to alloHCT immediately after BV. Six patients progressed while on BV treatment and some received additional chemotherapy. We did not exclude these patients from the analysis, as they were still given BV and achieved response to BV initially.

It is not surprising that we found improved 2-year PFS and cumulative incidence of relapse/progression in the BV group, as multiple previous reports show that improved disease status at transplantation and HCT-CI are associated with improved PFS after alloHCT [6,12,16-18]. We understand that this study is not a prospective trial and, therefore, suffers from biases inherent in retrospective analyses. However, this comparison was performed on 2 consecutive case series of patients from 2003 to 2008 (pre-BV era) and 2009 to 2012 (post-BV area). Essentially, this reflects actual practice patterns occurring at our institution for the past 10 years and shows that alloHCT outcomes have improved in the BV era. OS did not change significantly at the 2-year time point. Of the 7 deaths in the BV group, 2 were due to disease progression, 2 due to GVHD, 1 due to infection, and 2 due to cardiovascular events (presumed long-term complications of radiation therapy). Of the 17 deaths in the no-BV group, 10 were due to disease progression, 4 due to GVHD, 1 due to infection, and 2 due to other causes. If the improvement in relapse rate continues after the 2-year time point, it is very likely we will see an improvement in OS, as most of the deaths in the no-BV group were due to disease progression. We will continue to follow these patients and it is possible that we will be able to see improvement in OS at the 3- or 5-year time points.

Although our 2-year PFS estimate of 59.3% is less striking than the 1-year PFS of 92.3% seen in our initial report on BV salvage before RIC-alloHCT [5], we felt it important to update our initial observations for increased accuracy resulting from longer follow-up, to evaluate outcomes in a more homogenous patient population, and to compare the outcomes of BV patients to a BV-naïve case series. There have been few other reports on BV before alloHCT [19,20], and our current study represents the largest series of patients with the longest follow-up successfully undergoing RIC-alloHCT after BV therapy. The patients in our BV and no-BV groups are well matched at diagnosis and at relapse, and diverge in their disease characteristics only after BV treatment. We believe these data demonstrate that BV allows clinicians to improve disease status at transplantation, median HCT-CI, and peri-transplantation severe toxicities. These, in turn, are associated with an improvement in 2-year PFS and cumulative incidence of relapse/progression. For patients with relapsed/refractory HL who are considered candidates for RIC-alloHCT, BV is a reasonable option as a bridge to RIC-alloHCT.

ACKNOWLEDGMENTS

This work was supported by National Cancer Institute of the National Institutes of Health grant P30 CA33572 and the Tim Nesvig Lymphoma Research Fund. R.C. is supported by the National Cancer Institute of the National Institutes of Health grant K12CA001727. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health.

The authors thank Dr. Eileen Smith, Dr. Chatchada Karanes, Dr. Ryotaro Nakamura, Dr. Pablo Parker, Dr. Margaret O'Donnell, Dr. Amrita Krishnan, Dr. Ricardo Spielberger, and Dr. Samer Khaled for their dedication to treating these complex patients. They also thank Michelle Mott, Tanya Paris, and Bernie Pulone, for their assistance with collecting and managing the study data.

Presented as a poster at the 2013 American Society of Hematology Meeting in New Orleans, Lousiana.

Financial disclosure: R.C., T.S., and A.N. are consultants for Seattle Genetics and have received research funding from Seattle Genetics.

Conflict of interest statement: There are no potential conflicts of interest beyond those listed in the financial disclosures.

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